

REMARKS

Claims 1 and 3-23 are pending in this application. No amendments are presented herein.

Claims 1 and 3-23 are rejected under 35 U.S.C. §103(a) for alleged obviousness by U.S. Patent No. 6,458,383 to Chen et al ("Chen 383"), the combination of Chen 383, U.S. Patent No. 5,508,040 to Chen et al. ("Chen 040") and U.S. Patent No. 5,840,329 to Bai ("Bai"), and further in view of U.S. Patent No. 6,309,853 to Freidman et al. ("Freidman"), U.S. Patent No. 5,876,742 to Cochrum et al. ("Cochrum"), U.S. Patent No. International PCT/US84/01827 ("Robinson"), and U.S. Patent No. 5,801,154 to Baracchini et al. ("Baracchini"). Applicants respectfully request reconsideration of the rejection, as the cited art does not render the claims obvious.

As best understood, the Office Action appears to assert that the present invention is obvious in view of the cited art, on the basis that:¹

- 1) Chen 383 allegedly teaches administration of an oral formulation comprising a first population of cationic particles comprising an oligonucleotide and a penetration enhancer (specifically, a fatty acid said to be caprylic acid, lauric acid, or capric acid, and a bile salt said to be cholic or deoxycholic acid) a chelating agent (said to be EDTA, citrate or salicylate) that are released at a first location in the intestine, and another population of particles that is the same or different from the first, and that comprises a penetration enhancer and a delayed

¹ Applicants cannot immediately ascertain precisely how the various cited references are being applied in the current rejection. For example, the Office Action in the paragraph bridging pages 3 and 4 states that Chen 383 teaches compositions comprising a population of cationic particles comprising an oligonucleotide and a penetration enhancer (which, as Applicants point out *infra*, is incorrect), whereas in its argument on pages 5-7, the Office Action appears to cite Chen 383 (with Chen 040 and Bai) only for allegedly teaching "first and second populations of particles for delayed drug release in a mammal including humans," apparently relying upon Friedman et al. and/or Baracchini et al. for disclosure of oligonucleotides or antisense oligonucleotides (and other elements of the dependent claims). For the purposes of this response, Applicants assume that the Office Action intends to apply the cited art in accordance with its characterizations of the same on pages 3-5.

release coating or matrix which are released at a location in the intestine downstream from the first location (Office Action at page 3-4);

2) Chen 040 allegedly teaches a first and second population of particles, which second population of particles comprises penetration enhancers that are released at a time later in the intestinal tract (Office Action at page 4); and

3) Bai allegedly teaches a first and second population of particles, which second population of particles comprises penetration enhancers that are released at a time later in the intestinal tract (Office Action at page 4).

The Friedman, Cochrum, Robinson and Baracchini references are further said to teach various elements of the dependent claims. Specifically, the Office Action states that Friedman allegedly teaches particles for delayed release of biological substances comprising antisense oligonucleotides and further comprising alginate (citing “especially” col. 43-45 and col. 47); Cochrum allegedly teaches particles for the controlled or delayed release of biological substances in an organism that comprise poly-L-lysine and alginate (citing “especially” col. 6, lines 53-55; col. 8, line 9-col. 9, line 17); Robinson allegedly teaches carrier particles for delayed release of biological substances comprising bioadhesive agents and further comprising a steroid anti-inflammatory agent (citing page 6, lines 14-18; page 11, line 24-page 13, line 13); and Baracchini allegedly teaches the incorporation of 2'-methoxyethoxy sugar moieties into antisense oligonucleotides for enhancing their stability (citing col. 2, line 58-col. 3, line 14).

The Present Claims Are Not Obvious In View Of Chen 383

The Office Action asserts that Chen 383 discloses the administration of:

... an oral formulation comprising a population of cationic particles comprising an oligonucleotide and a penetration enhancer which are released at a first location in the intestine, and which penetration enhancer comprises a fatty acid (caprylic, lauric, capric), a bile acid (cholic, deoxycholic), a chelating agent (EDTA, citrate, salicylate), and another population of particles comprising a penetration enhancer and a delayed release coating or matrix, and polyethylene glycol, which second population is the same or different composition of the first, and is released at a location in the intestine that is downstream from the first location.

In support of its assertion, the Office Action cites the “entire document, especially col. 7-8, 9-15, 19-23, 28-32, claims 1, 18, 24, 56, 70, 71, 91).”² (Office Action at pages 3-4). Applicants respectfully disagree with the Office Action’s assessment of the teaching of Chen 383.

Chen 383 generally discloses a dosage form comprising a composition of: (a) a therapeutically effective amount of low molecular weight heparin; (b) a bile salt or bile acid; (c) at least one surfactant selected from hydrophilic surfactants, lipophilic surfactants, and mixtures thereof; and a means for delaying release of the composition from the dosage form following oral administration. Chen 383 further discloses that release in its dosage form can be in a “staged” or “pulsatile” fashion (see col. 7, lns. 60-65; col. 8, lns. 33-35), and, in a separate passage, states that the dosage form is not limited with respect to “size, shape or general configuration,” but can “comprise, for example, a capsule, a tablet or a caplet, or a multiparticulate carrier comprising a plurality of particles, granules, beads, pellets, or mixtures thereof, that may or may not be encapsulated.” (see col. 19, lns. 6-11). However, Applicants do not find the description of two populations of oligonucleotide-containing particles described in the Office Action. Indeed, the word “oligonucleotide” does not appear anywhere in Chen 383. Rather, Chen 383 clearly is directed to compositions for the delivery of low molecular weight heparins. Although the Chen 383 specification broadly states at col. 7, lns. 1-4 that its active agent can include “other macromolecules such as peptides, proteins, peptidomimetics, cytokines, nucleotides, nucleosides, genetic materials, toxoids, serum vaccines or combinations thereof,” there is no further mention of any such macromolecules, and no suggestion at all of oligonucleotides.³ Moreover, each of the examples of Chen 383 are directed to heparin compositions. Thus, contrary to the assertion of the Office Action,

² As a preliminary matter, Applicants respectfully point out that reliance on the claims of a reference for prior art purposes is improper. See *In re Benno*. 226 U.S.P.Q. 683.

³ Chen 383 recites “genetic materials,” but does not provide any definition for what such “genetic materials” are.

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Chen 383 does not disclose "... an oral formulation comprising a population of cationic particles comprising an oligonucleotide and a penetration enhancer...".

Moreover, even if Chen 383 did disclose oligonucleotides for use in its formulations (and it does not), it would still not render the present claims obvious for at least the reason that the Office has not set forth any legally sufficient motivation to select the various aspects of Chen 383 and combine them together in the manner asserted by the Office Action. Indeed, the only motivation for selecting the particular disclosures in Chen 383 is found in Applicants' disclosure, which discloses a specific problem addressed by the present invention.

The present invention provides a solution to the problem posed by the rapid absorption and loss of penetration enhancer from the intestine following administration of oligonucleotides, which is disclosed by Applicants in the present specification. Significantly, this problem is not disclosed or suggested by Chen 383 (or indeed any of the cited art, or any combination thereof). The present invention provides a solution to this problem by providing a second population of carrier particles comprising a penetration enhancer and a delayed release coating or matrix, wherein said penetration enhancer is released at a second location in said intestine downstream from said first location. It is well settled that where the claimed invention solves a problem, the discovery of the source of the problem and its solution are considered to be part of the "invention as a whole" under 35 U.S.C. §103. *In re Kaslow*, 707 F.2d 1366, 217 U.S.P.Q. 1089 (Fed. Cir. 1983); *In re Nomiya*, 509 F.2d 566, 184 U.S.P.Q. 607 (C.C.P.A. 1975); and *In re Sponnoble*, 405 F.2d 578, 160 U.S.P.Q. 237 (C.C.P.A. 1979). Accordingly, absent a disclosure or suggestion in Chen 383 of the problem that the present invention addresses, the present claims cannot be considered obvious in view of this reference. Inasmuch as Chen 383 contains no such suggestion, it cannot be said to render the present claims obvious. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §103.

**The Present Claims Are Not Obvious In View Of The Combination of Chen 383,
Chen 040 and Bai**

Neither Chen 040 nor Bai cure the deficiencies of Chen 383. The Office Action asserts on page 4 that Chen 040 teaches:

... a first and second population of particles, which second population of particles comprises penetration enhancers that are released at a time later in the intestinal tract (abstract; figures 1-3; col 3, line 36-col. 4, line 16; col. 5, lines 10-38; claims 1, 16 and 18).⁴

However, Applicants can find no teaching of the use of a penetration enhancer in Chen 040. Chen 040 discloses dosage forms consisting of two or more populations of pellets or particles that each contains a core containing the drug, and a water soluble osmotic agent. Each core is enclosed by a water-impermeable, water insoluble polymer film. The film of each population of particles incorporates a different amount of a “hydrophobic, water insoluble agent” (or “hydrophobic agent”) *for the specific purpose of altering the permeability of the polymer film, and thus providing different rate of release of drug from the core*. See Chen 383 at col. 2, lns. 34-39 and 46-48; col. 3, lns. 55-57; col. 4, lns. 2-5. Accordingly, Chen 040 does not teach the use of penetration enhancers as recited in the present claims. Moreover, Chen 040 does not teach or suggest the inclusion of oligonucleotides in its formulations, and, most significantly, Chen 040 contains no suggestion at all of the problem to which Applicants’ invention is addressed. Accordingly, the Chen 040 reference fails to cure the deficiencies of the Chen 383 reference.

The Office Action further asserts on page 4 that Bai teaches:

... a first and second population of particles, which second population of particles comprises penetration enhancers that are released at a time later in the intestinal tract (see col 1, line 36-col. 3, line 43; claim 1).⁵

⁴ Again, Applicants respectfully point out that patent claims are not properly applied as prior art. See footnote 1, *supra*.

⁵ Again, Applicants respectfully point out that patent claims are not properly applied as prior art. See footnote 1, *supra*.

However, again contrary to the assertion of the Office Action, Applicants can find no disclosure or suggestion of the use of penetration enhancers in Bai. Bai discloses a pulsatile delivery system comprising a plurality of particles for delivery of a drug in any of a number of desired patterns. Specifically, the Bai formulation consists of an external coating layer consisting of a water-insoluble, water permeable polymer and a water-permeable polymer, and a structured inner core containing one or more controlled release layers, with or without the active agent, with optional interposed swelling layers. Bai neither discloses nor refers to penetration enhancers, or the inclusion of oligonucleotides in its formulations.⁶ And, like the Chen 383 and Chen 040 references, Bai contains no suggestion whatsoever of the problem to which the present application is addressed. Accordingly, the Bai reference fails to cure the deficiencies of the Chen 383 reference.

From the discussion above, it can be seen that the Chen 040 and Bai references do not add to the teaching of Chen 383. Accordingly, Applicants respectfully assert that the present claims are not obvious in view of the combination of the Chen 383, Chen 040 and Bai references, and respectfully request withdrawal of this rejection under 35 U.S.C. §103.

The Secondary References Fail To Cure The Deficiencies Of The Chen 383, Chen 040 And Bai References.

The secondary references fail to cure the deficiencies of the Chen 383, Chen 040 and Bai references. None of the references, individually or in combination, disclose the problem to which the present application is directed. Absent such a suggestion, there is no legally sufficient motivation to pick and choose from among the various teachings of the cited art to assemble elements of the present claims. Indeed, it is settled law that such a hindsight approach is not a proper basis for a rejection under 35 U.S.C. §103. *In re*

⁶ The passage of Bai cited by the Office Action is entirely within the section entitled "Background of the Invention," which is a summary of the art prior dosage forms prior to the Bai invention. Each of these dosage forms is described in terms of its release profile, and there is no disclosure or suggestion of the use of penetration enhancers or oligonucleotides in connection with any of these dosage forms.

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Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). Accordingly, for the reasons discussed above, Applicants respectfully request withdrawal of this rejection.

The claims presently pending are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned representative at (215) 665-2158 to clarify any unresolved issues raised by this response.

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